Journal of Cardiology Cases 12 (2015) 145–149

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

Coronary angioscopic imaging of in-stent restenosis after biolimus-eluting coronary stent implantation

Shigenori Ito (MD, PhD, FJCC)*, Tomoaki Saeki (MD, PhD)

Division of Cardiology, Nagoya City East Medical Center, Nagoya, Japan

ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form 3 June 2015
Accepted 8 June 2015

Keywords:
Drug-eluting stent
Intravascular ultrasound
Optical coherence tomography
Coronary angioscopy
In-stent restenosis
Imaging

ABSTRACT

A 69-year-old man underwent repeat percutaneous coronary intervention for in-stent restenosis in the obtuse marginal artery 8 months after biolimus-eluting stent (2.5 × 28 mm Nobori stent, Terumo, Tokyo, Japan) implantation. Coronary angiography showed focal stenosis in the distal part of the stent. Intravascular ultrasound revealed low echoic heterogeneous intimal tissue. Optical coherence tomography also revealed a heterogeneous finding classified as a layered pattern. Coronary angioscopy detected a white mass with a paste-like appearance at the stenosis extending around the in-stent restenosis as a thin membrane where stent strut could be seen transparently. A small part of the mass was swinging in the blood stream. Coronary angioscopic imaging was beneficial for the understanding of the suspected mechanism and feature of the in-stent restenosis after second-generation stent implantation, which was apparently different from neointimal hyperplasia after bare-metal stent implantation.

<**Learning objective:** The learning objectives of this case report include understanding the mechanism of in-stent restenosis after second-generation drug-eluting stent implantation by showing the coronary angioscopic imaging beyond the other intravascular imaging. In particular, this case can make the general and interventional cardiologists learn that the mechanism of in-stent restenosis <1 year is different from that after bare-metal stent implantation.>

Introduction

The use of drug-eluting stents (DES) has dramatically decreased the restenosis rate. However, despite DES implantation, restenosis still occurs at an incidence rate of 5–10%. The mechanism of in-stent restenosis (ISR) might differ between DES and bare-metal stents (BMS) potentially because of the polymer or drug on the stent strut in DES. The mechanism of ISR after biolimus-eluting stent (BES) implantation, a second-generation stent, is not well known. We experienced a case of ISR 8 months after BES implantation that could be evaluated by coronary angioscopy (CAS) besides intravascular ultrasound (IVUS) and optical coherence tomography (OCT).

Case report

A 69-year-old man underwent coronary angiography for angina pectoris. His medical history included old anteroseptal and inferior myocardial infarction, vasospastic angina, chronic atrial fibrillation, type 2 diabetes mellitus, and dyslipidemia. He had undergone percutaneous coronary intervention (PCI) for the coronary stenoses in the left anterior descending coronary artery (LAD) and obtuse marginal artery (OM) 8 months previously. A BES was implanted for a calcified lesion in the LAD after rotational ablation (Nobori 2.5 × 28 mm, Terumo, Tokyo, Japan) and for the tandem lesion in the OM after balloon pre-dilataion (Nobori 2.5 × 28 mm) (Fig. 1a and b). After 8 months the angina pectoris recurred and he underwent coronary angiography and an ISR was detected in the Nobori stent implanted in the OM. On angiographic examination, the ISR was morphologically eccentric and focal (lesion length 7.7 mm) in the distal part of the stent, where minimal lumen diameter (MLD) existed at baseline (Fig. 1c). No ISR was observed in the LAD. His medication included aspirin 100 mg, clopidogrel sulfate 75 mg, warfarin 2 mg, benidipine hydrochloride 4 mg, diltiazem hydrochloride R 100 mg, atorvastatin calcium hydrate 10 mg, isosorbide dinitrate 40 mg, sitagliptin phosphate hydrate 50 mg, and voglibose 0.9 mg per day at the time of PCI for ISR. Dual antiplatelet therapy was maintained after index PCI. Two months later, he underwent balloon angioplasty for the ISR by using a 2.5 × 13 mm cutting balloon followed by a paclitaxel-eluting balloon SeQuent Please® (2.5 × 26 mm; B. Braun, Melsungen,

* Corresponding author at: Division of Cardiology, The Junshukai Medical Foundation Higashiyama Clinic, 5-103 Higashiyama-dori, Chikusa-ku, Nagoya-shi, Aichi-ken 464-0807, Japan. Tel.: +81 52 781 1235; fax: +81 52 789 7000.
E-mail address: shigeito918@gmail.com (S. Ito).

http://dx.doi.org/10.1016/j.jccase.2015.06.004
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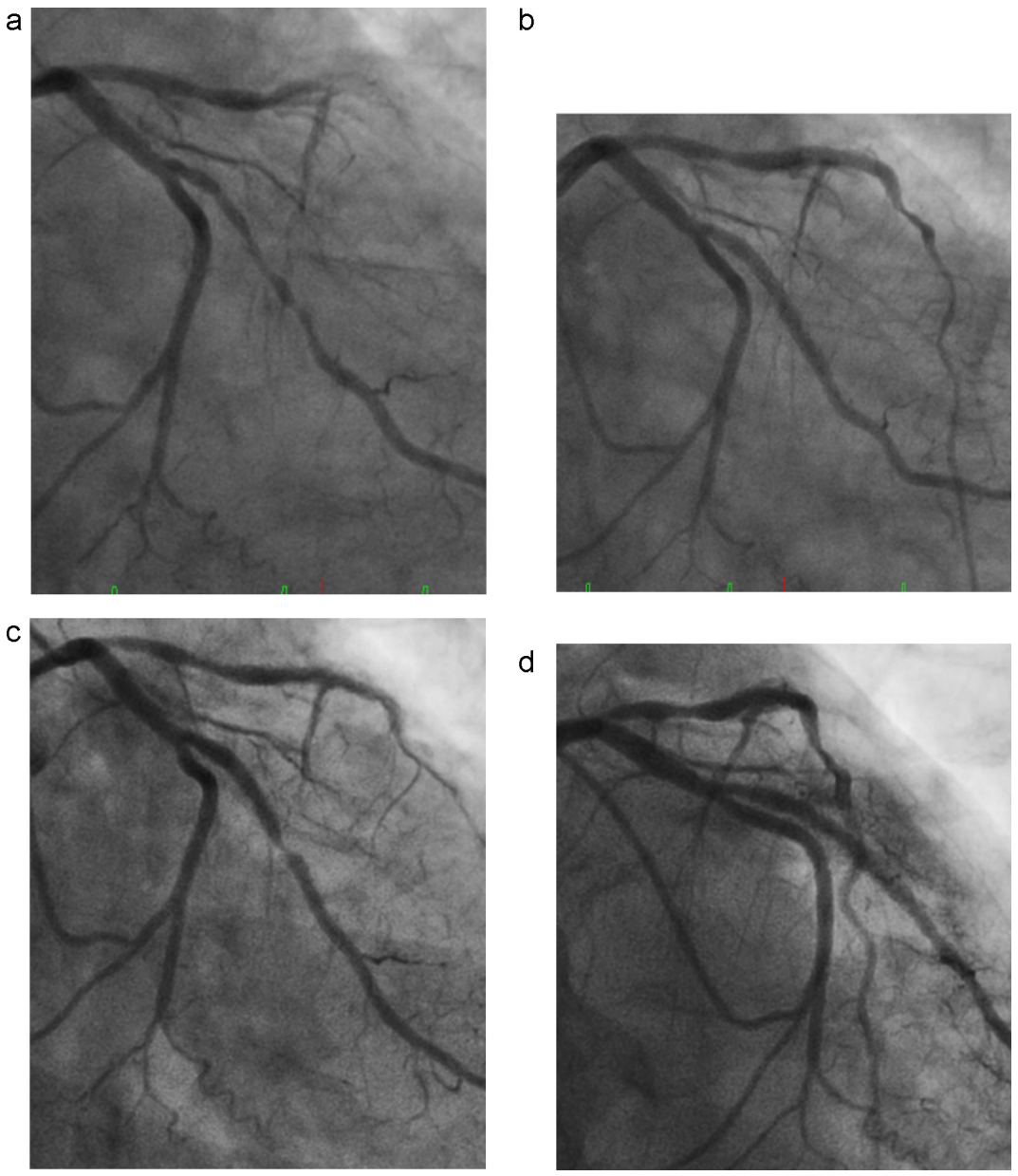

Fig. 1. Coronary angiograms. (a) Before index percutaneous coronary intervention (PCI). A tandem lesion in the obtuse marginal artery was found. No calcification or thrombus was detected. (b) After index PCI. Good result was obtained after 2.5 × 28 mm Nobori stent implantation. (c) At follow-up. Focal in-stent restenosis was detected in the distal part of the previously deployed Nobori stent in a minimal lumen diameter site. (d) After cutting balloon dilatation followed by paclitaxel-eluting balloon OptiCross® (2.5 × 26 mm). Stent-like result was found with no dissection or thrombus.

Germany) under IVUS (OptiCross™ coronary imaging catheter, Boston Scientific Corp., Natick, MA, USA), OCT (Ilumen™ OCT Imaging System, St. Jude Medical Inc., St. Paul, MN, USA), and CAS guidance (Smart-i™, iHeartmedical, Tokyo, Japan). No improvement in angiographic findings was observed in the follow-up angiography. IVUS revealed a heterogeneous low echoic plaque with a little lower echogenicity near the stent struts (Fig. 2a). OCT (Fig. 2b) revealed a heterogeneous intimal hyperplasia component (classified as layered [1]). Delayed healing and inter-strut halo in the stent were observed in the area without ISR (Fig. 2c). CAS showed a white mass that looked like paste extending around ISR as a thin membrane where stent strut could be seen transparently (Fig. 3a and b). A small part of mass was swinging in the blood stream (Fig. 3c). The intensity of the intimal hyperplasia on IVUS and OCT is apparently lower than that usually found in ISR after BMS implantation, which usually shows homogenous high intensity. Neointimal tissue could be easily dilated at 6 atm. The OCT finding after cutting balloon dilatation showed no residual plaque or intimal flaps in the stent indicating that the plaque was detached and flown away distally after balloon dilatation (Fig. 2d). We decided to treat this lesion with a paclitaxel-eluting balloon SeQuent Please®, not with a stent, based on its stent-like result. Final coronary angiograms showed excellent results without any residual stenosis or slow flow/distal embolism (Fig. 1d).

Discussion

In this case, we demonstrated an interesting CAS image suggesting the mechanism of ISR after BES stent implantation.

This finding in association with IVUS and OCT images is different from that of ISR after BMS implantation, where intimal

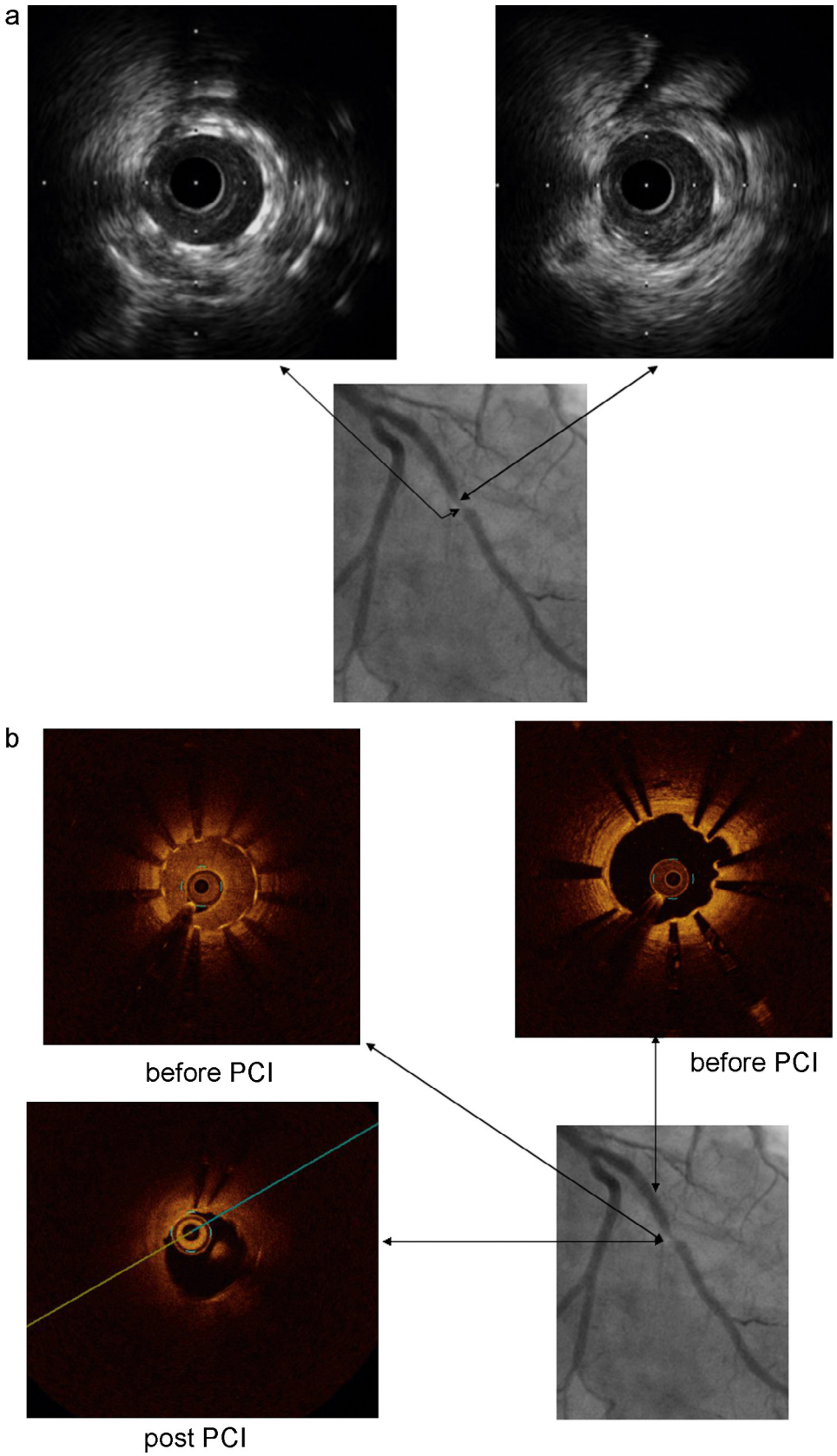

Fig. 2. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT). Each black arrow indicates the location of IVUS or OCT image in the incorporated angiography. (a) IVUS before percutaneous coronary intervention (PCI). Two representative images are shown. A low echoic heterogeneous plaque was detected. (b) OCT before and after PCI. At in-stent restenosis site, a heterogeneous (layered) intimal hyperplasia component was detected before PCI, where no residual intimal hyperplasia was found at in-stent restenosis site. At reference site before PCI, delayed healing and inter-strut halo in the stent were observed in the area without in-stent restenosis.

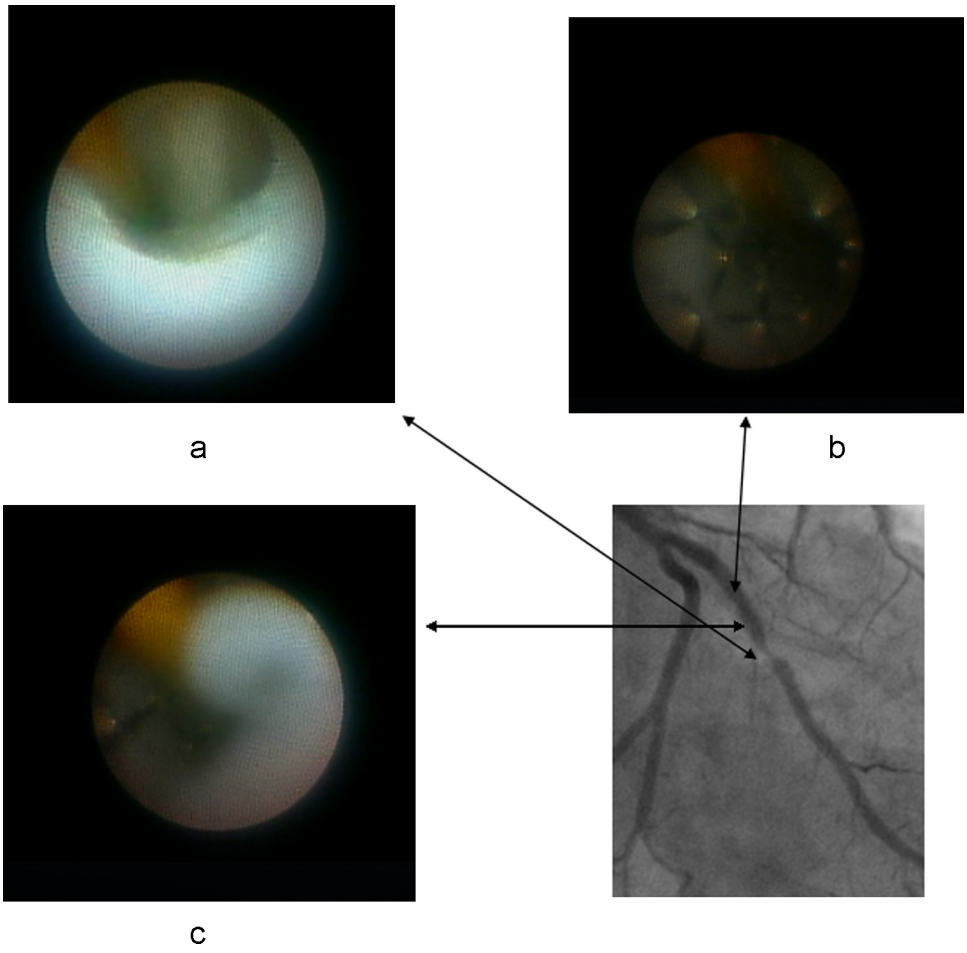

Fig. 3. Coronary angioscopy (CAS) before percutaneous coronary intervention (PCI). Each black arrow indicates the location of CAS image in the incorporated angiography. (a) At the minimal lumen diameter site. The vascular lumen was narrowed by the white paste-like soft tissue. (b) Delayed healing of the nonrestenotic site. Similar tissue was detected in the lesion near the in-stent restenosis. Stent strut could be seen transparently. (c) The swinging piece of neointimal tissue component.

hyperplasia by smooth muscle cells occurs after BMS implantation [2]. Although, unfortunately, we did not perform plaque retrieval as a pathological specimen, white thrombus or inflammatory products or their complexes were possibly [3–5] present.

Late and very late stent thrombosis or restenosis (>1 year) is a challenging problem in patients who underwent DES implantation. It may occur at a low annual incidence of 0.2–0.6%, however it could be lethal if it occurs. Nagai et al. reported on patients with DES ISR lesions who showed heterogeneous intimal hyperplasia assessed by OCT and histopathology [6]. Thus, its mechanism, prevention, and treatment are widely investigated. However, ISR <1 year after DES implantation had not been focused on intensively.

Araki et al. [7] characterized the in-stent neointimal tissue components according to the restenosis phase by using radio-frequency signals from 40-MHz IVUS, (iMAP-IVUS; Boston Scientific Corp.) in 37 angina patients (37 lesions) who underwent repeated PCI for the treatment of DES ISR. The percentage of lipid components and relative necrotic volume were greater in the late (>1 year) ISR group than in the early (≦1 year) ISR group. Tsujita et al. [8] also reported similar results. DES implantation would be associated with iMap-derived necrotic and less-fibrotic neointimal formation. Itoh et al. [4] assessed the ISR image produced by OCT for tissue heterogeneity and neointimal hyperplasia in 100 angiographic ISR lesions by using the normalized standard deviation of OCT signal intensity (OCT-NSD) observed in neointimal hyperplasia tissue. ISR lesions were divided into homogeneous ($n = 48$) and nonhomogeneous ($n = 52$) image groups. The prevalence of DES was 48% in the nonhomogeneous group and 29% in the homogeneous group ($p = 0.05$). The OCT-NSD value in the nonhomogeneous group was significantly higher than that in the homogeneous group. Pathological tissue showed fibrin thrombi with infiltrating macrophages in 12 cases of nonhomogeneous ISR. The nonhomogeneous ISR image visualized by OCT may show chronic inflammation and fibrin thrombi. Oikawa et al. [5] directly compared IVUS and CAS imaging findings with histopathological assessment of DES in first-generation sirolimus-eluting stent (SES). Within 1 year, 21 SES- and 8 BMS-related ISR occurred (10.8 versus 7.5 months, respectively). Directional coronary atherectomy was performed for histological examination. Thrombus and fibrin depositions detected by either CAS or histopathology were observed more frequently in the SES than in the BMS group (92.3% vs. 25.0%, $p = 0.007$). CAS did not reveal red thrombus, but showed white thrombus in six SES and two BMS cases (46.2% vs. 25.0%, $p = 0.597$). Histological findings demonstrated various patterns after SES including thrombus, fibrin, inflammatory infiltrate, and collagen-matrix rich tissue, while thrombus component was not detected in BMS. Thus, SES ISR may be frequently associated with thrombus component. Hayashi et al. [3] reported a similar phenomenon in a patient with ISR 6 months after everolimus-eluting stent (EES) implantation. Diagnostic angiography demonstrated focal ISR in the long multiple EESs.

OCT before angioplasty showed the complex features of this stenotic lesion, which was successfully dilated with a cutting balloon. The whitish material obtained by using a distal protection device was composed of fibrin thrombi with neutrophils and small pieces of mature fibrocellular neointima. Recently, Shibuya et al. [9] revealed natural history of heterogeneous intimal hyperplasia assessed by OCT. Based on the nonhomogeneous features of IVUS and OCT images, and the white paste-like CAS image, fibrin thrombi with infiltrating inflammatory cells were the suspected pathological cause. The mechanism of ISR in this case could be based on the delayed healing after stent implantation. As a limitation of this case report, we did not perform histopathological examinations and tissue characterization of the neointimal tissue by using iMAP. Although this case report might lack novel IVUS and OCT findings, however, strength would exist in that CAS, which gives color, softness, and motion, and could be contrasted with IVUS and OCT by direct visualization in vivo.

Conflict of interest

The authors declare that there is no conflict of interest.

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